CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Grünenthal GmbH/Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	Not available	
Name of Active Ingredient(s)	Tapentadol HCl (also known as CG5503 and R331333)	

Protocol No.: R331333-PAI-3004 (KF5503/34)

Title of Study: A Randomized, Double-Blind, Active-Control, Parallel-Group, 90-Day Safety Study of CG5503 (Tapentadol HCl) Immediate Release (IR) or Oxycodone IR in Subjects With Chronic Pain From Low Back Pain or Osteoarthritis of the Hip or Knee

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Publication (Reference): None

Study Period: 31 July 2006 to 17 July 2007 | **Phase of Development:** 3

Objectives: The primary objective of the study was to evaluate the safety profile of tapentadol IR 50 mg or 100 mg taken every 4 to 6 hours as needed over the long-term exposure of 90 days. The secondary objectives included estimation of the relative safety profile of tapentadol and oxycodone; evaluation of the symptoms of withdrawal from opioids following discontinuation of study drug using the Clinical Opiate Withdrawal Scale (COWS) and the Subjective Opiate Withdrawal Scale (SOWS) questionnaires; evaluation of symptoms using the Patient Assessment of Constipation Symptoms (PAC-SYM), a single question regarding vomiting, and a sleep assessment; assessment of pain intensity over the 90-day study period; and assessment of the Patient Global Impression of Change (PGIC) as recorded at the end of treatment regardless of when this occurred.

Methodology: This was a Phase 3, randomized, double-blind, active-control, parallel-group, multicenter, safety study of tapentadol IR or oxycodone HCl IR in subjects with a clinical diagnosis (present for at least 3 months) of chronic low back pain or chronic pain from osteoarthritis of the knee or hip requiring opioid therapy. Approximately 875 subjects were to be randomly assigned in a 4:1 ratio to receive either tapentadol IR (700 subjects) or oxycodone HCl IR (175 subjects), respectively. The study randomization was stratified by country and prior opioid experience. In addition to the study drug, subjects who were taking non-opioid analgesia at study entry at a stable dose for at least the 30 days before screening were able to continue that regimen. Subjects who required analgesia beyond the study drug and their regular non-opioid analgesia regimen were permitted to take rescue medication, acetaminophen or ibuprofen, for no more than 3 days in 1 week. Subjects randomized to tapentadol IR took 50 or 100 mg every 4 to 6 hours as needed to provide adequate pain control with acceptable tolerability. Subjects randomized to oxycodone HCl IR took 10 or 15 mg every 4 to 6 hours as needed to provide adequate pain control with acceptable tolerability. The study included a screening period, washout period, double-blind treatment period, end-of-treatment visit, and a follow-up period.

A subject completed the study if he or she completed the 90 days of double-blind treatment and the follow-up visit. Subjects who prematurely discontinued for any reason were not considered as having completed the study. Subjects who discontinued after randomization were not replaced.

Number of Subjects (planned and analyzed): Planned: 875 subjects (700 tapentadol IR and 175 oxycodone HCl IR). Analyzed for safety and efficacy (took at least one dose of study drug): 849 (679 tapentadol IR and 170 oxycodone HCl IR). The target for this safety study was to have 300 to 500 subjects exposed to the tapentadol IR for at least 30 days and 100 subjects exposed for at least 90 days. The analyses included 484 subjects exposed for at least 30 days and 318 subjects exposed for at least 90 days.

Diagnosis and Main Criteria for Inclusion: Study subjects were men and nonpregnant, nonlactating women at least 18 years of age, with moderate to severe pain (≥4 on the 11-point numeric rating scale [NRS]) who required daily doses of analgesic medication for chronic pain that was consistent with or made them candidates for treatment at Step 2 or higher of the World Health Organization (WHO) Pain Relief Ladder.

Subjects were excluded if they had seizure disorder or epilepsy or if they had laboratory values reflecting moderate or severe renal insufficiency or hepatic impairment.

Test Product, Dose, and Mode of Administration, Batch No.: Tapentadol IR 50 mg capsules (over-encapsulated tablets) for oral use. Batch numbers: PD-2230, PD-2231, PD-2119, and PD-2085. Capsules were orally administered. The HCl salt form of the drug substance was used, but the doses are expressed using free base weight.

SYNOPSIS (CONTINUED)

Reference Therapy, Dose, and Mode of Administration, Batch No.: Oxycodone HCl IR 5 mg or 10 mg capsules (over-encapsulated tablets) for oral use. Batch numbers 5 mg: PD-2240, PD-2317, PD-1981, PD-2117, and PD-2197. Batch numbers 10 mg: PD-2241, PD-2318, PD-1982, PD-2118, and PD-2198. The HCl salt form of the drug substance was used, and the doses are expressed using salt weight.

Duration of Treatment: One 90-day treatment period, during which tapentadol IR (50 mg or 100 mg) or oxycodone HCl IR (10 mg or 15 mg) was administered every 4 to 6 hours as needed. At the end of treatment, study drug was stopped without tapering. The study duration, including the time from the screening visit through the follow-up visit, was approximately 123 days or 18 weeks.

Criteria for Evaluation:

Efficacy: Efficacy was recorded using pain intensity and PGIC assessments recorded by the subject. Pain intensity was assessed using the 11-point NRS at baseline (Day 1) and at each double-blind-treatment visit (Days 15, 29, 43, 57, 71, and 91) and assessing the subject's pain for the previous 24 hours. The 7-point, numeric PGIC was assessed at the end-of-treatment visit (Day 91) or at time of early discontinuation.

Safety: Adverse events were recorded from the time of the informed consent form was signed until the last study procedure was completed. Changes in clinical laboratory results, physical examination, vital sign measurements, and 12-lead electrocardiogram (ECG) measurements were assessed. In addition, urine pregnancy tests and urine drug screenings were performed to determine continued eligibility in the study. Additional safety evaluations included COWS, SOWS, PAC-SYM, and vomiting and sleep assessments.

Pharmacokinetics: No study drug concentrations were assessed.

Pharmacogenomics: No pharmacogenomic evaluations were planned for this study.

Statistical Methods:

Sample Size Determination: The desired number of tapentadol IR subjects (700 subjects) was based on the incidence of discontinuation from previous long-term studies in subjects with chronic pain to obtain 300 to 500 subjects exposed to tapentadol IR for at least 30 days and 100 subjects exposed for at least 90 days. The desired number of oxycodone HCl IR subjects (175 subjects) was based on a previous 4-week study in subjects with osteoarthritis to provide approximately 90% power to detect a difference in the constipation incidence. Therefore, a 4:1 tapentadol:oxycodone randomization ratio was used.

Efficacy: Descriptive statistics for the value and the change from baseline of pain intensity were provided at each assessment timepoint and at endpoint. Descriptive statistics were presented for each treatment group.

Safety: Adverse events were summarized by treatment group and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence of the treatment-emergent adverse events (TEAEs) in the gastrointestinal (GI) system, such as nausea, vomiting, and constipation, were summarized and compared among treatment groups using the Cochran-Mantel-Haenszel test. Time to the first treatment-emergent nausea, vomiting, and constipation was summarized descriptively, presented in Kaplan-Meier plot, and compared using log-rank test. Odds ratios of the event incidence were calculated for tapentadol IR versus oxycodone HCl IR. Subjects who experienced a serious adverse event or who discontinued from the study due to an adverse event were summarized. Clinical laboratory results were summarized using descriptive statistics by treatment group, and the number and percentage of subjects with laboratory values outside the normal range were presented. Twelve-lead ECG, vital signs, and physical examination results were also summarized by treatment group using descriptive statistics. Possible opiate withdrawal effects were assessed using descriptive statistics of the COWS and SOWS scores and treatment comparisons in terms of opiate withdrawal effects were performed using the Cochran-Mantel-Haenszel test and analysis of variance (ANOVA) model. Sleep-pattern changes and the incidence of vomiting and constipation were summarized descriptively.

Pharmacogenomics: No pharmacogenomic analyses were performed.

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SUMMARY - CONCLUSIONS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

The demographic and baseline characteristics were balanced across the treatment groups. Most subjects were white (83.9%). Approximately half of the subjects across both treatment groups were women (54.9%), and the majority of subjects were <65 years of age (76.1%). In total, 82.1% of subjects were categorized as having severe baseline pain intensity (pain intensity ≥6 using 11-point NRS); the overall median pain intensity score at randomization was 7 on 11-point NRS.

EFFICACY RESULTS:

The study was not designed to evaluate efficacy as a primary endpoint. However, efficacy measurements were performed, and descriptive analyses showed efficacy similar to oxycodone HCl IR, a known opioid analgesic. The mean pain intensity scores at endpoint were 4.9 and 5.2 in the tapentadol IR and the oxycodone HCl IR groups, respectively. In addition, PGIC results were comparable between the tapentadol IR and oxycodone HCl IR treatment groups over time. At the end of the treatment period, 43.1% of the tapentadol IR group and 41.9% of the oxycodone HCl IR subjects reported "Much improved" or "Very much improved."

SAFETY RESULTS:

During the study, tapentadol IR was well tolerated with a safety profile similar to the oxycodone HCl IR comparator, a μ-opioid agonist. Prospectively defined adverse event comparisons with oxycodone HCl IR indicated improved GI tolerability with tapentadol IR. Central nervous system (CNS) tolerability was similar.

The overall percentage of subjects with TEAEs for the oxycodone HCl IR group was 82.9% compared with 76.3% in the tapentadol IR group. The most common TEAEs (incidence >10% in either treatment group) were nausea, vomiting, constipation, dizziness, headache, somnolence, and pruritus. Comparing the incidence of these TEAEs for the tapentadol IR group with those for the oxycodone HCl IR group, the incidence was lower in the tapentadol IR group for nausea, vomiting, constipation, and pruritus and was similar for dizziness, headache, and somnolence.

For nausea, vomiting, and constipation and for the composite event of nausea/vomiting, a comparison between tapentadol IR and oxycodone HCl IR using the Cochran-Mantel-Haenszel test showed a significantly lower incidence in the tapentadol IR group (all p-values <0.001, not adjusted for multiplicity). The percentage of subjects with nausea, vomiting, constipation, or the composite of nausea/vomiting was significantly lower in the tapentadol IR group (18.4%, 16.9%, 12.8%, and 28.0%, respectively) than in the oxycodone HCl IR group (29.4%, 30.0%, 27.1%, and 45.9%, respectively). For all of these events, the odds ratios were below 1.0, and the upper bounds of the corresponding confidence intervals did not exceed 1.0, reflecting significantly lower incidence of these events in the tapentadol IR versus the oxycodone HCI IR group. In addition, the percentages of subjects in the safety analysis set with at least 1 TEAE of nausea, vomiting, or constipation that was severe in intensity were lower in the tapentadol IR group (0.9%, 1.6%, and 0.9%, respectively) than in the oxycodone HCl IR group (3.5%, 2.9%, and 3.5%, respectively).

Examination of TEAE incidence by day revealed that, as expected, the incidence of nausea and vomiting tended to diminish with duration of therapy, whereas the incidence of constipation persisted throughout the course of therapy. While the tapentadol IR group had generally a lower incidence by study day than the oxycodone HCl IR group, the patterns were similar on this daily measure.

One subject died during screening (cerebrovascular accident); none died during the treatment or posttreatment period (30 days from last exposure). Serious TEAEs were reported by 5 subjects (0.7%) in the tapentadol IR group and 3 subjects (1.8%) in the oxycodone HCl IR group. All serious TEAEs were either unrelated or unlikely related to study drug. The serious TEAEs experienced by subjects in the tapentadol IR group included acute myocardial infarction, myocardial infarction, thalamic infarction, transient ischemic attack, and bronchitis viral. One serious, related, unexpected adverse event of drug withdrawal syndrome was reported by a subject in the tapentadol IR group. It was not documented as treatment emergent because it occurred more than 2 days after the last study drug intake.

Of subjects who were randomized and received at least 1 dose of study medication, 57.6% in the tapentadol IR group and 50.6% in the oxycodone HCl IR group completed the study. The most common reason for discontinuation was adverse events (21.2% in the tapentadol IR group and 31.2% in the oxycodone HCl IR group). The most common TEAEs leading to discontinuation were nausea, vomiting, constipation, and dizziness.

For the treatment period, examination of mean values over time did not reveal clear or consistent patterns for laboratory results, vital signs, or ECG values, and there was no apparent association of mean changes with tapentadol IR administration. Examination of individual abnormal values for laboratory results, vital signs, and ECG assessments revealed single occurrences of outlying values. TEAEs related to laboratory results, vital signs, and ECG assessments also occurred at a low incidence. In summary, the incidence of such single occurrences of variations was low and did not reveal a clear pattern.

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Assessment using the sleep questionnaire and PAC-SYM assessments indicated similar results for tapentadol IR and oxycodone HCl IR, whereas the vomiting questionnaire indicated an advantage for tapentadol IR over oxycodone HCl IR.

In this study, study drug was terminated without tapering. Based on COWS results, for subjects not taking opioids medication after discontinuation, those subjects taking tapentadol IR were significantly less likely to have withdrawal symptoms than those subjects taking oxycodone HCl IR. Considering adverse events of drug withdrawal syndrome for subjects in the tapentadol IR group, there was 1 serious adverse event (also mentioned above) and 8 nonserious TEAEs. This incidence (1.3%) was comparable to the incidence in the oxycodone HCl IR group (1.2%).

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Not applicable. Study drug concentrations were not determined in this study.

PHARMACOGENOMICS:

Not applicable, there was no pharmacogenomic component to this study.

CONCLUSION:

With a flexible dosing regimen that reflects the actual clinical use of centrally acting analgesics, tapentadol IR (50 or 100 mg every 4 to 6 hours, as needed) showed efficacy similar to oxycodone HCl IR (10 or 15 mg every 4 to 6 hours, as needed), a known opioid analgesic, for up to 90 days for the treatment of moderate to severe, chronic, low back pain or osteoarthritis pain of the hip or knee in an outpatient setting. Tapentadol IR was well tolerated with a safety profile similar to that of other centrally acting analgesics with μ-opioid activity. Prospectively defined adverse event comparisons with oxycodone HCl IR indicated improved GI tolerability with tapentadol IR. CNS tolerability was similar.

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SYNOPSIS (CONTINUED)

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